ABSTRACT

Proteolytic cleavage of the amyloid precursor protein (APP) by secretases leads to the release of a range of amyloid β (Aβ) peptides. Increased production of Aβ42 over Aβ40 and its subsequent aggregation into oligomers and plaques constitute a hallmark of Alzheimer’s disease (AD). While screening products of the ‘human chemical exposome’ for inducers of Aβ42 production, we observed that six triazines, among a panel of 37 of these widely used herbicides, induce a 2-10 fold increase in the production of extracellular Aβ42 in a variety of cell lines (N2A-APP695, CHO-7PA2, HEP293-APPsw), primary neuronal cell cultures and neurons differentiated from human iPSCs. Induction of Aβ42 production by these triazines requires the activity of both β - and γ-secretases, as revealed by specific inhibitors of these proteases. Analysis of the produced amyloids by immunoprecipitation followed by mass spectrometry shows enhanced production of peptides cleaved at positions 42 and 43, and reduced production of short peptides cleaved at positions 39, 38 and lower. Neurons derived from human iPSCs obtained from an AD patient with the APP K724N mutation produced more Aβ42 vs. Aβ40 than neurons derived from iPSCs obtained from healthy controls (APP WT). Triazines further enhanced the production of Aβ42 in both control and AD neurons. To identify the triazines responsible for enhanced production of Aβ42, we affinity purified the interacting proteins on diroopropionamide gels by affinity chromatography from mouse brains and N2A-APP695 cells. Triazines also shifted the cleavage pattern of alcaines (calysyntens), another family of γ-secretase substrates, suggesting a direct effect of triazines on γ-secretase rather than on its substrates. We conclude that some widely used triazines are able to enhance the production of toxic, aggregation prone Aβ42 and Aβ43 amyloids. These results suggest the possible existence of environmental ‘Alzheimerogenic’ products which may contribute to LOAD development. Such molecules could also be of use to create non-genetic AD models.

INTRODUCTION

Alkylaryl-triazines (Forty-Two Inducers) are a family of molecules triggering robust up-regulation of extracellular/secreted Aβ42 and increased Aβ42/Aβ40 ratio, similar to what is described in late onset AD (refs. 1,2). Our objective was to investigate whether such Aβ42 inducers are found among products of common exposure (‘Human Chemical Exposome’ (HCE)).

RESULTS

We screened 3500+ HCE products and detected a few Aβ42 inducers, including some triazine herbicides. Among 37 commercial triazines, 6 triggered Aβ42 production in various cell lines, primary neuron cultures and neurons derived from human iPSCs. Neurons derived from iPSCs from AD patients (APP-K724N mutation) showed increased Aβ42 production which was further enhanced by triazines or Aftin-5. These results, initially obtained by ELISA, were confirmed by immunoprecipitation/mass spectrometry identification of the complete range of secreted Aβ fragments.

CONCLUSION

(i) the Aftins, some triazines trigger a shift in the γ-secretase cleavage site preference at APP, leading to a relative increase in the production of longer, more aggregation-prone amyloids, (ii) the HCE contains products able to induce production of Aβ42, (iii) these molecules may constitute new pharmacological tools to develop chemoprevention/chemical animal models of AD, (iv) such potentially ‘Alzheimerogenic’ products may contribute to the development of late onset AD, (v) identification of environmental Aβ42 inducers may lead to further prevention approaches.

REFERENCES


CONTACT

<meier@manros-therapeutics.com>
Tel. +33 (0)6.88.69.39.34

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